Vitamin B12 Malabsorption Due to Intrinsic Factor Deficiency in Indian Subjects

By H. G. Desai and F. P. Antia

Sixteen patients (from Bombay) with severe vitamin B12 malabsorption due to intrinsic factor deficiency, presenting as subacute combined degeneration of the cord (7), tropical sprue (3), anemia (2), thyrotoxicosis (2), diabetes mellitus (1), and pain in the abdomen (1), are reported. The difficulties of establishing a definite diagnosis of pernicious anemia in Indian population are described. The lower incidence of circulating intrinsic factor antibody (IFA) in Indian patients with histamine-fast achlorhydria and poor vitamin B12 absorption is emphasized.

The necessity of separating atrophic gastritis, with severely impaired vitamin B12 absorption, from pernicious anemia on the basis of absence or presence of IFA in serum and/or gastric juice cannot be overemphasized.

Pernicious anemia was reported to be rare in blacks, Chinese, and Indians. These few case reports in studies from India did not show (1) improvement of poor, radioactive vitamin B12 absorption with administration of intrinsic factor or normal gastric juice, (2) atrophic gastritis on gastric biopsy, and (3) achlorhydria with adequate histamine stimulation. Poor vitamin B12 absorption corrected with intrinsic factor was observed in a patient with tropical sprue from South India, and the similarity of the stomach lesion of this disease to that of pernicious anemia was emphasized. Pernicious anemia in two Indians staying in Singapore and in a patient with thyrotoxicosis (from Bombay) showing circulating parietal cell antibody (PCA) and intrinsic factor antibody (IFA) were reported. Recently, pernicious anemia was diagnosed in two Indian patients staying in London, one of whom also had IFA in serum.

The object of this communication is to report our observations in 16 patients (from Bombay) with severe vitamin B12 malabsorption due to intrinsic factor deficiency studied over a period of 8 yr, indicating that pernicious anemia does occur in Indian population.

MATERIALS AND METHODS

The 16 patients studied presented with a variety of clinical diagnoses, including subacute combined degeneration of the cord (7), tropical sprue (3), anemia (2), thyrotoxicosis (2), diabetes mellitus (1), and pain in the abdomen (1). There were 12 males and four females. The average age of the patient was 49.2 (25–70) yr. Details of the neurological lesion in five of the seven patients with subacute combined degeneration of the cord have been described in a previous study.

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Submitted February 23, 1972; first revision April 18, 1972; second revision May 25, 1972; accepted May 29, 1972.

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Serum vitamin B₁₂ was estimated by a microbiological method using Euglena gracilis,¹² and serum folate was measured using Lactobacillus casei.¹³ PCA was detected by the complement fixation test.¹⁴ IFA in serum and intrinsic factor content of gastric juice were measured by the albumin-coated charcoal method.¹⁵ ⁵⁸Co-vitamin B₁₂ absorption was measured, after administering 1 µg vitamin B₁₂ containing 1 µCi radioactivity, by either the Schilling test¹⁶ or the fecal excretion method.¹⁷ The test was repeated with normal human gastric juice in patients showing poor vitamin B₁₂ absorption. Fecal fat estimation was performed by the wet method¹⁸ on 3-days stool collection, with patients consuming 75–100 g fat/day. d-Xylose excretion in 5-hr urine was estimated after feeding a 5 g dose.¹⁹ Gastric mucosal biopsy from the fundus or body of the stomach and jejunal biopsy from the upper jejunum were obtained with a Crosby-Kugler capsule. Sections were stained with hematoxylin and eosin and classified as described in previous studies.²⁰ ²¹ Gastric analysis was performed by modified subcutaneous histamine test, administering subcutaneously 2.4 mg of histamine acid phosphate.²² Maximal acid output (MAO) was calculated by the method of Card and Marks.²³ Achlorhydria was considered to be present when the pH of gastric juice was 6 or above, or a fall in pH was less than 1.

RESULTS

The relevant clinical data and investigations are shown in Table 1.

Hematologic Studies

Hemoglobin was less than 9 g/100 ml in five (31.3%) patients only, and anemia was the presenting symptom in two of them. Bone marrow was megaloblastic in eight out of 12 patients, as some (cases 1 and 8) had previously received injections of vitamin B₁₂. Serum vitamin B₁₂ was 80 µg/ml or less in ten out of 11 patients, and serum folate was less than 4 µg/ml in five out of ten patients studied.

Gastric Studies

In all patients except one (case 14), MAO was less than 2.0 meq/hr, and achlorhydria was noted. Severe atrophic gastritis was observed in all 13 patients in whom biopsy was performed. None showed gastric atrophy as described in pernicious anemia patients from Western countries. Circulating PCA was present in five out of seven (71.4%) patients, and IFA was present in two out of 13 (15.4%) patients in whom these tests were performed. Both patients showing circulating IFA had presented with thyrotoxicosis. ⁵⁸Co-vitamin B₁₂ urinary excretion was less than 5% (Schilling test), and fecal absorption was less than 20% in all patients. On repeating the test with intrinsic factor (gastric juice), absorption of vitamin B₁₂ improved appreciably in 14 patients, while two (cases 8 and 9) showed a minimal rise.

Small Intestinal Studies

Steatorrhea was present in 11 patients, and several of them had normal bowel habit. d-Xylose malabsorption was present in seven, and jejunal mucosa showed partial villus atrophy in eight patients.

Family History

The details of the family history in case 1 have been previously published.²⁴ None of the other patients gave a positive family history for pernicious anemia or subacute combined degeneration of the cord.
DISCUSSION

Diagnosis of adult pernicious anemia is dependent on showing megaloblastic bone marrow, low serum vitamin B₁₂ level, severe atrophic gastritis or gastric atrophy, histamine-fast achlorhydria, absent or subnormal intrinsic factor content of gastric juice, poor radioactive vitamin B₁₂ absorption improving with intrinsic factor, presence of PCA and IFA in serum and/or gastric juice of the majority of patients, and at times a positive family history. The diagnosis of pernicious anemia is definite in those of our patients (1–7, 10–16) showing considerable rise in vitamin B₁₂ absorption on administration of intrinsic factor (gastric juice) but is uncertain in those (8, 9) not exhibiting an appreciable rise (of vitamin B₁₂ absorption). In a patient with pernicious anemia, failure of correction of vitamin B₁₂ malabsorption with intrinsic factor may be due to either the presence of IFA in gastric juice or salvia, or to damage of ileal mucosa secondary to (1) vitamin B₁₂ deficiency (corrected with vitamin B₁₂ therapy) or (2) occult tropical sprue in our population (corrected with antibiotics). In this study, the rise of vitamin B₁₂ absorption with intrinsic factor was subnormal in three patients (cases 2, 14, and 15) and was negligible in another two (cases 8 and 9). In these two patients, the presence of IFA in gastric juice cannot be blamed for vitamin B₁₂ malabsorption, as even serum IFA is rare in Indian subjects. Moreover, damage to ileal mucosa sec-

\[ \text{Fig. 1. Classification of chronic gastritis and pernicious anemia.} \]

\[ \text{VITAMIN B₁₂ MALABSORPTION} \]

\[ \text{NORMAL} \]
\[ \text{MILD-MODERATE (II)} \]
\[ \text{SEVERE IMPAIRED} \]
\[ \text{PERNICIOUS ANEMIA (IV)} \]

\[ \text{OLD-NEW CONCEPT} \]
\[ \text{CONCEPT} \]

\[ \text{NORMAL} (1) \]
\[ \text{MILD-MODERATE (II)} \]
\[ \text{SEVERE IMPAIRED} \]
\[ \text{PERNICIOUS ANEMIA (IV)} \]

\[ \text{VITAMIN B₁₂ ABSORPTION} \]
\[ \text{NORMAL} \]
\[ \text{IMPAIRED} \]

\[ \text{% OF ADMINISTERED DOSE: EXCRETION IN URINE} > 10\% 5 - 10\% < 5\% \]
\[ \text{ABSORPTION BY FECAL COLLECTION} > 50\% 29 - 49\% < 29\% \]

\[ \text{IFA = INTRINSIC FACTOR ANTIBODY IN SERUM AND/OR GASTRIC JUICE} \]
### Table 1. Clinical Features and Investigations

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Hb (g/100 ml)</th>
<th>Bone Marrow</th>
<th>Serum B&lt;sub&gt;12&lt;/sub&gt; (μg/ml)</th>
<th>Serum Folate L. casei (mg/ml)</th>
<th>MAO</th>
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| Normal value | >13.0 | >80 | >4 | >10 |

* Intrinsic factor content of gastric juice (U/hr): case 1, 28; case 2, 42; case 4, 91; case 6, 28; case 16, 160.
† After B<sub>12</sub> injection.
‡ After antibiotic.

Secondary to vitamin B<sub>12</sub> deficiency is also unlikely, as one patient (case 8) had already received injection of vitamin B<sub>12</sub> prior to the test. In all probability, the rise of vitamin B<sub>12</sub> absorption with intrinsic factor was prevented by an associated ileal lesion, as steatorrhea was observed in both of them.

In our Indian population, the definite diagnosis of pernicious anemia is difficult to establish because: (1) macrocytic anemia, megaloblastic bone marrow, and low serum vitamin B<sub>12</sub> levels are frequently not observed due to the common practice of injecting vitamin B<sub>12</sub> and B complex as “tonic” for any illness; (2) improvement of radioactive vitamin B<sub>12</sub> absorption when administered with intrinsic factor may not be observed due to the prevalence of occult or manifest ileal lesion of tropical sprue; and (3) facilities for radioactive vitamin B<sub>12</sub> absorption and detection of gastric antibodies are limited. Our observations in 16 patients studied during the last 8 yr emphasize that pernicious anemia does occur in Indian population but is diagnosed rarely because the above-mentioned factors prevent a definite diagnosis and perhaps also because the majority of our hospital population studied is below 50 yr of age.

Several features in our pernicious anemia patients differ from those observed in Western countries (1) Eight out of 16 patients in the present study were 45 yr of age or less. (2) Gastric mucosal atrophy was not observed in any patient.
VITAMIN B₁₂ MALABSORPTION

In 16 Patients With Pernicious Anemia

<table>
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<th>Schilling Test (% excretion)</th>
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N, normoblast; Meg, megaloblast; MAO, maximal acid output; SAG, severe atrophic gastritis; PCA, parietal cell antibody; IFA, intrinsic factor antibody; IF, intrinsic factor; PVA, partial villus atrophy; SCD, subacute combined degeneration of cord.

(3) The incidence of PCA is comparable, but the incidence of IFA is appreciably low in patients with pernicious anemia, thyrotoxicosis, diabetes mellitus, and iron deficiency anemia from India as compared to those from Britain, North America, and Australia. IFA was present in only two patients presenting as thyrotoxicosis but was absent in 20 patients with histamine-fast achlorhydria, 315 with iron deficiency anemia, and 400 with diabetes mellitus. Family history is negative in most of our patients. These observations in a genetically different population from that studied in Western countries suggest that the majority of our patients (except two with IFA) are of atrophic gastritis, since despite poor vitamin B₁₂ absorption the IFA is rare, and resemble patients with atrophic gastritis showing poor vitamin B₁₂ absorption and absence of circulating IFA (classified as pernicious anemia) in studies from the West.

The ultimate lesion of gastric mucosa is perhaps determined by two factors: (1) damage to mucosa by environmental factors, and (2) a specific, inherited defect perpetuating damage in gastric mucosa. In all probability, environmental factors are responsible for the lesion of atrophic gastritis, while environmental factors and a specific inherited defect determine the lesion of pernicious anemia. The separation of atrophic gastritis and pernicious anemia in studies from Western countries solely on the basis of arbitrarily determined...
levels of radioactive vitamin B12 absorption is artificial (Fig. 1). Patients with atrophic gastritis and severely impaired vitamin B12 excretion (less than 5% on Schilling’s test) should not be classified as cases of pernicious anemia, and this diagnosis should be restricted to those with the above criteria and IFA in serum and/or gastric juice.

REFERENCES

24. Desai, H. G., Borkar, A. V., Dighe,
VITAMIN B₁₂ MALABSORPTION


Vitamin B₁₂ Malabsorption Due to Intrinsic Factor Deficiency in Indian Subjects

H. G. Desai and F. P. Antia